REMARKS

Claims 1-22 are presently pending in the Application. Claims 15, 21 and 22 are withdrawn from consideration. By this Amendment, Claims 1, 8, 16, 18 and 19 are amended and Claims 9-11 are canceled. Support for the amendments to the Claims can be found generally throughout the Specification and Claims as filed and particularly in the Examples.

Election

In Section 6 of the Office Action it is stated that a telephonic election of Group 1, claims 1-14 and 16-20 was made by Applicant's Attorney. That election is affirmed.

Objections to the Specification

In Section 9 of the Office Action it is pointed out that the application lacks section headings. Amendments to the the Specification have been made adding standard headings. Withdrawal of the Objection is respectfully requested.

In Section 10 of the Office Action, the Examiner states that She cannot find the conditions for Example 3 in any of the Hampton Research protein crystal formulations. Applicants do not know what materials the Examiner was searching for the conditions in Example 3, however, they are readily available. Submitted herewith is a printout of 48 different protein crystallization screens available from Hampton Research. The copyright notice on the bottom includes 2000-2006. Number 35 on this printout is the one used in Example 3. Accordingly, this objection should be withdrawn.

Objections to the Claims

In Section 11 of the Office Action, Claim 8 is objected to as it presents an amino acid sequence which lacks an corresponding sequence in the Sequence Listing. A substitute Sequence Listing is submitted herewith with the appropriate sequence added as SEQ ID NO. 6. The omission was inadvertent and support for the sequence is found on page 7, lines 32-33 and page 9, lines 11-12. Corrections to the specification are also made by this Amendment to refer to the appropriate SEQ ID NO. Withdrawal of the Objection is respectfully requested.

In Section 12 of the Office Action, Claim 8 is objected to as missing a conjunction. Claim 8 is amended to, among other things, correct this deficiency. Withdrawal of the Objection is respectfully requested.

Claim Rejections Under 35 USC §112 Second Paragraph

In Section 14, the Office Action states that, with regard to claims 2-7, His B10 may not be present in certain insulin analogues. Claim 1, from which Claims 2-7 depend, has been amended such that B10 must be histidine. Hence, the rejection should be withdrawn.

In Section 15 the Office Action states that there is no antecedent basis in Claim 1 for the use of the plural "molecules" in claims 2-7. This rejection is respectfully traversed. It is a well known tenet of claim construction that "an", or "a" as Claim 1 is currently amended, can be singular or plural. Accordingly, as "a human insulin analog" in Claim 1 is properly interpreted to mean one or more of the human insulin analog molecules, it is respectfully submitted that there is sufficient antecedent basis in Claim 1 for plural "molecules" in claims 2-7 and the rejection should be withdrawn.

In Section 16 of the Office Action, it is stated that in Claims 12-14 it is unclear if Applicants are claiming an insulin crystal in an acceptable formulation which will retain its crystalline state. Claim 12, from which Claims 13 and 14 depend, provides the limitation that the pharmaceutical preparation comprises at least one *crystal*. Accordingly, if the preparation is not one which is capable of maintaining the crystallization state for at least some period of time then such a preparation would not be encompassed by Claims 12-14. Accordingly, Claims 12-14 are not indefinite and the rejection should be withdrawn.

In Section 17 of the Office Action, Claim 16 is rejected as omitting an allegedly essential element, that being something for the zinc-free, amorphous powder to be dissolved in. Claim 16 has been amended to specifically include a liquid as a limitation. Hence, the rejection should be withdrawn.

In Section 18 of the Office Action, claims 19 and 20 are rejected as being indefinite as to whether the pH range is applicable or required of both precipitants. Applicants do not fully understand the question. These claims describe a buffered system. Ammonium dihydrogenphosphate and diammonium dihydrogenphosphate are in equilibrium, so the pH range is applicable to both. By this Amendment, Claim 19 is amended to replace "or" with "/" to further clarify that the same equilibrium is occurring in both claim 19 and Claim 20. Clam 18 has also been amended to make clear that diammonium hydrogenphosphate is one of the possible precipitants. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections Under 35 USC §112, First Paragraph

In Section 20 of the Office Action, Claims 1-14 and 16-20 are rejected as not being enabled for crystals of insulin analogs other than those having Lys at B3 and Glu at B29. Claim 1, on which the others are dependent, has been amended to claim a crystal of a human insulin analog having Lys at

B3 and Glu at B29, rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

Also in Section 20 of the Office Action, Claims 1-14 are rejected as lacking written description. Again, Claim 1, on which the others are dependent, has been amended to claim a crystal of a human insulin analog having Lys at B3 and Glu at B29 and where B1 is Phe. Applicants contend that the Lilly case cited by the Office Action has no application to claims 1-14 as in the Lilly case the patent at issue did not have the structure or formula of the claimed human DNA sequence other than that it encoded a given human amino acid sequence and the rat cDNA sequence. That is not at all the situation with the instant claims where the Crystals are described by exact amino acid sequences and as being present in the space group R3 (No. 146) with the cell axes A = 81.5 Å ± 1Å and C = 33.3 Å ± 1 Å. Applicants submit that this is the structure or formula required by Lilly and the written description requirement is met. Accordingly, withdrawal of the written description rejection with respect to claims 1-14, as amended, is respectfully requested.

In Section 21 of the Office Action, Claims 2-7 are rejected as lacking written description as there are allegedly no actual molecular atomic coordinates or a three-dimensional drawing of the claimed features. Applicants submit that the Specification as filed adequately describes the amino acid sequence, conditions for crystallization and at, for instance, page 11, line 18 - page 12, line 13 and in Example 4, there is given specific x-ray crystallographic data of the crystals of the present invention and a discussion of how that data differs from the data one would expect from insulin crystals containing zinc. Applicants are unaware that the Written Description requirement of 35 U.S.C. §112,1st paragraph has a necessity for proof as the Office Action seems to be requiring. What the written description requirement does necessitate is an adequate description of the invention. Applicants submit that the data in the instant Specification adequately describes the instant invention

by using x-ray crystallographic scientific terms for insulin hexamer assembly and x-ray structural characterization recognized by those skilled in the art and request that this rejection be withdrawn.

Claim Rejections Under 35 USC §102

In paragraph 23 of the Office Action, Claims 12-14 are rejected over Ertl because the group R3 would allegedly cease to exist in a pharmaceutical composition. This Rejection is respectfully traversed. As discussed in response to the 35 USC §112, Second Paragraph rejection in paragraph 16 of the Office Action, Claims 12-14 require at least one crystal of the human insulin analog of Claim 1, along with the group R3. Accordingly, Applicants respectfully request that this rejection be withdrawn.

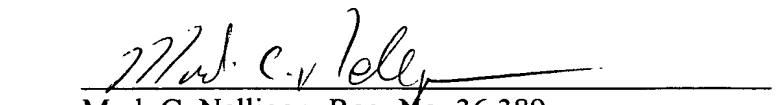
In the light of the above, it is respectfully submitted that all objections and rejections be withdrawn, and the Claims be allowed to issue.

The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account no. 18-1982.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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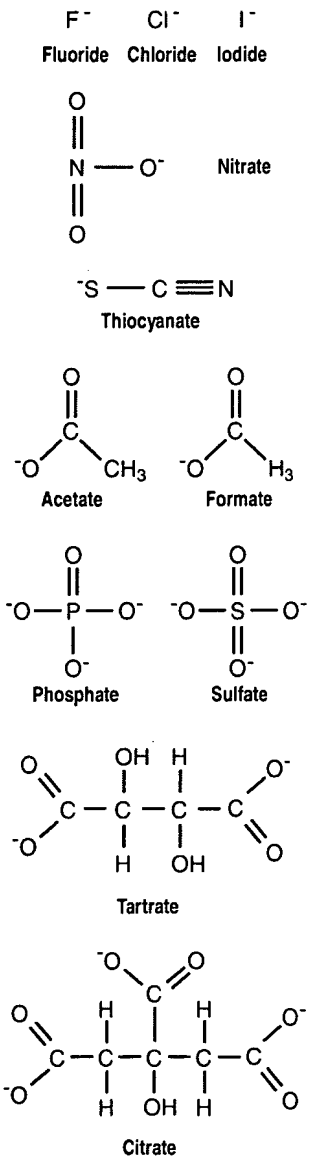
PEG/Ion Screen™

HR2-126 Reagent Formulation

Tube #	Salt	Tube #	Polymer	Tube #	pH ◊
1.	0.2 M Sodium fluoride	1.	20% w/v Polyethylene glycol 3,350	1.	7.3
2.	0.2 M Potassium fluoride	2.	20% w/v Polyethylene glycol 3,350	2.	7.3
3.	0.2 M Ammonium fluoride	3.	20% w/v Polyethylene glycol 3,350	3.	6.2
4.	0.2 M Lithium chloride	4.	20% w/v Polyethylene glycol 3,350	4.	6.8
5.	0.2 M Magnesium chloride hexahydrate	5.	20% w/v Polyethylene glycol 3,350	5.	5.9
6.	0.2 M Sodium chloride	6.	20% w/v Polyethylene glycol 3,350	6.	6.9
7.	0.2 M Calcium chloride dihydrate	7.	20% w/v Polyethylene glycol 3,350	7.	5.1
8.	0.2 M Potassium chloride	8.	20% w/v Polyethylene glycol 3,350	8.	7.0
9.	0.2 M Ammonium chloride	9.	20% w/v Polyethylene glycol 3,350	9.	6.3
10.	0.2 M Sodium iodide	10.	20% w/v Polyethylene glycol 3,350	10.	7.0
11.	0.2 M Potassium iodide	11.	20% w/v Polyethylene glycol 3,350	11.	7.0
12.	0.2 M Ammonium iodide	12.	20% w/v Polyethylene glycol 3,350	12.	6.2
13.	0.2 M Sodium thiocyanate	13.	20% w/v Polyethylene glycol 3,350	13.	6.9
14.	0.2 M Potassium thiocyanate	14.	20% w/v Polyethylene glycol 3,350	14.	7.0
15.	0.2 M Lithium nitrate	15.	20% w/v Polyethylene glycol 3,350	15.	7.1
16.	0.2 M Magnesium nitrate hexahydrate	16.	20% w/v Polyethylene glycol 3,350	16.	5.9
17.	0.2 M Sodium nitrate	17.	20% w/v Polyethylene glycol 3,350	17.	6.8
18.	0.2 M Potassium nitrate	18.	20% w/v Polyethylene glycol 3,350	18.	6.8
19.	0.2 M Ammonium nitrate	19.	20% w/v Polyethylene glycol 3,350	19.	6.2
20.	0.2 M Magnesium formate dihydrate	20.	20% w/v Polyethylene glycol 3,350	20.	7.0
21.	0.2 M Sodium formate	21.	20% w/v Polyethylene glycol 3,350	21.	7.2
22.	0.2 M Potassium formate	22.	20% w/v Polyethylene glycol 3,350	22.	7.3
23.	0.2 M Ammonium formate	23.	20% w/v Polyethylene glycol 3,350	23.	6.6
24.	0.2 M Lithium acetate dihydrate	24.	20% w/v Polyethylene glycol 3,350	24.	7.9
25.	0.2 M Magnesium acetate tetrahydrate	25.	20% w/v Polyethylene glycol 3,350	25.	7.9
26.	0.2 M Zinc acetate dihydrate	26.	20% w/v Polyethylene glycol 3,350	26.	6.4
27.	0.2 M Sodium acetate trihydrate	27.	20% w/v Polyethylene glycol 3,350	27.	8.0
28.	0.2 M Calcium acetate hydrate	28.	20% w/v Polyethylene glycol 3,350	28.	7.5
29.	0.2 M Potassium acetate	29.	20% w/v Polyethylene glycol 3,350	29.	8.1
30.	0.2 M Ammonium acetate	30.	20% w/v Polyethylene glycol 3,350	30.	7.1
31.	0.2 M Lithium sulfate monohydrate	31.	20% w/v Polyethylene glycol 3,350	31.	6.0
32.	0.2 M Magnesium sulfate heptahydrate	32.	20% w/v Polyethylene glycol 3,350	32.	6.0
33.	0.2 M Sodium sulfate decahydrate	33.	20% w/v Polyethylene glycol 3,350	33.	6.7
34.	0.2 M Potassium sulfate	34.	20% w/v Polyethylene glycol 3,350	34.	6.8
35.	0.2 M Ammonium sulfate	35.	20% w/v Polyethylene glycol 3,350	35.	6.0
36.	0.2 M Sodium tartrate dibasic dihydrate	36.	20% w/v Polyethylene glycol 3,350	36.	7.3
37.	0.2 M Potassium sodium tartrate tetrahydrate	37.	20% w/v Polyethylene glycol 3,350	37.	7.4
38.	0.2 M Ammonium tartrate dibasic	38.	20% w/v Polyethylene glycol 3,350	38.	6.6
39.	0.2 M Sodium phosphate monobasic monohydrate	39.	20% w/v Polyethylene glycol 3,350	39.	4.7
40.	0.2 M Sodium phosphate dibasic dihydrate	40.	20% w/v Polyethylene glycol 3,350	40.	9.1
41.	0.2 M Potassium phosphate monobasic	41.	20% w/v Polyethylene glycol 3,350	41.	4.8
42.	0.2 M Potassium phosphate dibasic	42.	20% w/v Polyethylene glycol 3,350	42.	9.2
43.	0.2 M Ammonium phosphate monobasic	43.	20% w/v Polyethylene glycol 3,350	43.	4.6
44.	0.2 M Ammonium phosphate dibasic	44.	20% w/v Polyethylene glycol 3,350	44.	8.0
45.	0.2 M Lithium citrate tribasic tetrahydrate	45.	20% w/v Polyethylene glycol 3,350	45.	8.4
46.	0.2 M Sodium citrate tribasic dihydrate	46.	20% w/v Polyethylene glycol 3,350	46.	8.3
47.	0.2 M Potassium citrate tribasic monohydrate	47.	20% w/v Polyethylene glycol 3,350	47.	8.3
48.	0.2 M Ammonium citrate dibasic	48.	20% w/v Polyethylene glycol 3,350	48.	5.1



◊ Measured pH at 25 ° C

PEG/Ion Screen contains forty-eight unique reagents. To determine the formulation of each reagent, simply read across the page.

34 Journey
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